DEKA IN MEDICINE

Case report

A complex case of severe thrombocytopenia in systemic lupus erythematosus complicated by Corynebacterium spp. infection

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ABSTRACT

BACKGROUND: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune inflammatory disease the course of which is still indefinite. Thrombocytopenia concurrent with Corynebacterium spp.—an infrequent complication in SLE patients—is seldom reported.

CASE A 34-year-old female was admitted for continuous bleeding from the gums that had been ongoing for three days. The patient had been suffering from SLE since 2018 and took immunosuppressive medication regularly. The anemia, lymphocytopenia, and severe thrombocytopenia were shown in her laboratory tests. Besides, the infection of Corynebacterium spp. was detected in the patient. In fact, hematologic abnormalities and infections in SLE patients usually mutually overlap for the reason that these conditions possess the potential to influence each other. Infection can be both the cause and result of hematologic abnormalities in SLE. Thus, the pathophysiology of hematologic abnormalities in SLE patients can often be related to the use of immunosuppressive drugs. However, some theories suppose that increased SLE activity correlates with infection occurrence in SLE—even without the use of immunosuppressive drugs.

CONCLUSION Thrombocytopenia and Corynebacterium spp. infection in SLE patients is a case rarely reported, and establishing the diagnosis requires detailed examination.

KEYWORDS: SLE; hematologic abnormalities; infection; immunosuppressive drugs; thrombocytopenia.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease due to the formation of autoantibodies throughout the body. From that definition, therefore, SLE clinically manifests in multiorgan involvement—from more superficial organs like skin or mucosa, to internal organs such as the central nervous system, heart, lungs, kidneys, and bone marrow.[1] The hematologic disorder constitutes other frequent manifestations in SLE, with 82% of SLE patients in India showing hematologic abnormalities. Thrombocytopenia constitutes one of the frequent hematologic manifestations in SLE, occurring in 18% of cases.[2] Platelet counts are usually performed routinely by general practitioners in order to follow up on the patient and thus could be easily accessed at most healthcare facilities in Indonesia.[3] Thrombocytopenia reflects SLE disease activity and is, according to the disease criteria, considered a moderate to severe criterion. Platelet counts are also included in monitoring tools for SLE disease activity. Other literature categorizes thrombocytopenia as: mild (100,000 – 150,000

/mcL), seen in 25-50% of patients; and severe (<50,000 /mcL), in 10% of patients. This concern is usually due to immune-mediated platelet destruction most of the time.[4]

SLE patients are vulnerable to infections because 80% of SLE patients use steroids during the course of their disease.[4] Several factors that increase the risk of infection in SLE, apart from disease activity itself, include immune system disorders such as neutropenia and lymphopenia, as well as the use of immunosuppressive drugs like steroids.[2] Currently, there is no definitive evidence reporting which types of pathogens may potentially increase the risk of infection in SLE patients. Infections contribute to increased mortality during both the early and late stages of SLE treatment and are one of the leading causes of death in SLE patients, with an incidence ranging from 20% to 55%. Infection cases in SLE patients can increase morbidity. One study found that of 8,670 SLE patients followed for approximately 3 years, 2,123 patients experienced infection-related issues, with pneumonia being the leading cause of infection resulting in hospitalization (40.1%). The most common bacteria responsible for these infections were normal skin flora.[5]

Diphtheria is a respiratory infection with high morbidity and mortality rates and remains a significant health threat, particularly in developing countries. The World Health Organization (WHO) reported in 2017 that India had the highest number of diphtheria cases, with 5,293 cases, while Indonesia reported 954 cases, with East Java Province contributing the highest incidence.[6] Corynebacterium diphtheriae is the pathogenic bacterium most often responsible for diphtheria cases and is classified into Toxin and Non-Toxin groups based on the bacterium's properties.[7] Several studies have reported that, in addition to oropharyngeal abnormalities in cases of C. diphtheriae toxin group infections, hematologic manifestations such as thrombocytopenia can occur, though with a very low prevalence.[8,9] Therefore, hematologic abnormalities in diphtheria cases are still possible. SLE patients with compromised immune systems are at higher risk of C. diphtheriae infection, so when an infection occurs in SLE patients, hematologic abnormalities must be differentiated between manifestations of disease activity or signs of diphtheria infection.[10] Based on this, SLE patients are highly susceptible to infections from both pathogens and normal flora, necessitating comprehensive examination in immunocompromised patients. This article presents a case of severe thrombocytopenia in an SLE patient infected with Corynebacterium spp.

CASE PRESENTATION

We report a 34-year-old female patient with SLE who presented to our hospital because of an initial complaint of sudden gum bleeding, which started three days before our admission. Bleeding from her gums was continuous and oozing. The patient also reported trauma-free bruises on her arms and legs and bleeding in her left eye, which she had previously not noticed because her perception of vision had not changed. She also complained of a sore throat over the past 4 days, which was painful when swallowing food. Accompanying the sore throat was a change in voice (hoarseness) for the same duration. The patient reported no history of fever, cough, or shortness of breath before admission. On physical examination, whitish patches were seen on the tonsils that were bleeding easily; the patient was referred to the Tropical Medicine division for further management. The patient had been diagnosed with SLE in 2018 and had regularly visited the Rheumatology clinic at our hospital, receiving routine medication including Hydroxychloroquine 200mg once daily and CaCO3 500mg once daily. She had previously received Immuran but was taken off this due to a drop in her corpuscular elements of the blood. Steroid treatments were also stopped two years ago

when the patient was diagnosed with Glucocorticoid-Induced Osteoporosis (GIOP) and multiple compression fractures along the spine. The patient gave a history of monthly hospitalization for the last two months due to the same complaints of bleeding and had undergone platelet transfusions. She reported receiving all vaccinations during childhood. None of the family showed symptoms like sore throat, shortness of breath, or fever, nor did any neighbors near her residence; none of them had autoimmune diseases.

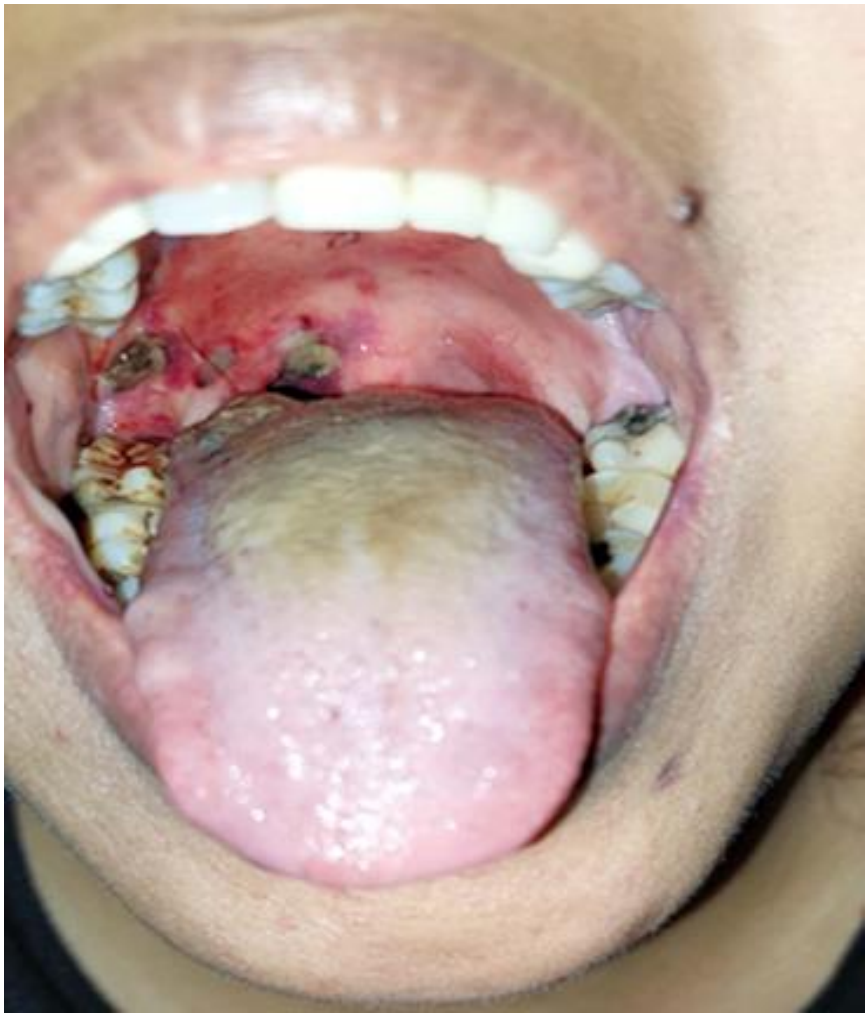

Figure 1. Oropharyngeal findings on the second day of hospitalization: notable pseudomembrane on the right tonsil.

On physical examination, the patient presented with anemic conjunctiva, left subconjunctival hemorrhage, gum bleeding, a pseudomembrane on the right tonsil, hyperemic pharynx, dullness in the Traube space, purpura over the bilateral upper extremities, and petechiae over the bilateral lower extremities. Laboratory tests revealed the following: decreased hemoglobin at 10.20 g/dL, increased white blood cells amounting to 11,790 μ/L, decreased platelet count of 1,000 μ/L, decreased hematocrit at 31.8%, increased neutrophils at 84.0%, decreased lymphocytes at 8.9%, and increased monocytes at 6.3%. Blood smear examinations showed normochromic anisopoikilocytosis in erythrocytes, with the presence of ovalocytes and macro-ovalocytes. The leukocyte count showed an overall increase in number with neutrophilia, lymphopenia, and hypersegmentation of neutrophils. Platelet count showed an overall decrease in number, along with the presence of macroplatelets. Gram staining from the throat swab revealed Gram-positive intracellular cocci, suggestive of a pathogen, and Neisser staining showed bacteria with metachromatic

granules indicative of Corynebacterium spp. Throat swab culture confirmed bacterial colonies, with Neisser staining revealing bacteria with metachromatic granules consistent with the morphology of Corynebacterium spp.

Figure 2. Clinical improvement of pseudomembrane following administration of ADS and antibiotics.

On day 1 of hospitalization, the platelet count was found to be 1,000/μL. On day 2, the patient experienced odynophagia and voice changes, and an oropharyngeal examination of the right side revealed detritus in the right tonsil (Figure 1). On day 3, the complaints persisted. By day 7, the odynophagia and voice changes were no longer present (Figure 2), but throat swab culture showed granulomatous bacteria typical of Corynebacterium spp. The treatment administered from day 1 to day 3 included Hydroxychloroquine 200 mg once daily, Methylprednisolone 125 mg once daily, and platelet transfusion of 6 packs per day. On day 3, Hydroxychloroquine was discontinued, and erythromycin 500 mg four times a day and Anti-Diphtheria Serum (ADS) 40,000 U were started for diphtheria treatment. On day 3, the platelet transfusions were stopped. From day 4 to day 7, the methylprednisolone dose was reduced to 16 mg three times daily, ADS was stopped, but erythromycin 500 mg four times daily was continued from day 3 to day 7.

DISCUSSION

In this reported case, the patient experienced severe thrombocytopenia accompanied by acute bleeding manifestations. Initially, the patient was reported as having SLE with severe disease activity based on platelet count. However, we classified the patient as having mild disease activity because there was no increase in complement levels or DNA binding in the patient. The patient was also reported not to meet the criteria for APS, so the patient was not diagnosed with secondary APS. Based on this data, the patient was re-evaluated for infection risk factors.

The patient reported experiencing a sore throat for the past 4 days, which became more painful when swallowing food. The sore throat was also accompanied by voice changes (hoarseness) for the same duration. Upon physical examination, a pseudomembrane was found on the right tonsil, which bled when removed, along with hyperemia of the pharynx. These physical examination findings were consistent with the pathognomonic sign of diphtheria, which includes the presence of a pseudomembrane—necrotic tissue and fibrin that is grayish-white in color, difficult to remove, and prone to bleeding. These findings, along with the sore throat described in the history, were indicative of pharyngeal diphtheria, which affects the tonsils and pharynx. Pharyngeal diphtheria has an incidence of around 75% and most commonly affects the adenoids, uvula, and soft palate. Symptoms typically begin with low-grade

fever, pseudomembrane, sore throat, odynophagia, dysphagia, voice changes, and regional lymphadenopathy.

The mechanism behind thrombocytopenia and C. diphtheriae infection in SLE patients, such as in this case, has not been definitively explained. However, several studies have reported thrombocytopenia in patients infected with diphtheria, particularly in those infected with toxin-producing C. diphtheriae. C. diphtheriae has two infection factors in humans: surface antigens and toxins produced by the bacteria. MSCRAMMS (Microbial Surface Components Recognizing Adhesive Matrix Molecules) first interact with the outer surface (skin/mucosa) of humans, allowing the bacteria to invade. Two antigen molecules, DIP2093 and DIP0733, have been reported to function during invasion by binding to Toll-like Receptor-2 (TLR-2) and the EGFR of nucleated cell surfaces. Once the bacteria are phagocytized by macrophages or surrounding cells, an inflammatory reaction occurs, leading to the production of pro-inflammatory cytokines such as IL-1β, IL-6, IL-18, NF-κB, and ROS.[7,11] Additionally, Mincle Fc and TLR-6 are expressed on the infected cells. The increase in ROS and nitric oxide (NO) in the cells as a reaction to the infection triggers apoptosis in those cells.[12] Besides surface antigens, C. diphtheriae can also invade and cause cell destruction using its toxin. The C. diphtheriae toxin is divided into two parts, Tox A and Tox B, each with distinct functions. Tox B binds to the surface receptor for the toxin, Heparin-Binding Epidermal Growth Factor-like Growth Factor (HB-EGFR), found in all nucleated cells, including macrophages, epithelial cells, and megakaryocytes. Once the toxin enters the cell and reaches the lysosome, Tox A exits the lysosome and binds to Elongation Factor-2 (EF-2), which acts as a NAD catalyst. The final product of this reaction is the EF-2+ADP ribosyltransferase+Nicotinamide complex, which inhibits protein synthesis in the cell, leading to apoptosis.[7,13] In macrophages infected with C. diphtheriae, there is an abnormal increase in Mincle Fc, particularly in macrophages located in the spleen. Mincle Fc plays a role in thrombocytopenia because it binds to surface antibodies that have attached to C. diphtheriae antigens. This activation increases platelet destruction in the spleen. These three mechanisms can occur simultaneously, leading to thrombocytopenia in patients infected with toxin-producing C. diphtheriae.[14]

In SLE patients with diphtheria infection, thrombocytopenia can occur, which may be difficult to differentiate between being caused by the diphtheria infection or as a manifestation of hematologic abnormalities in the patient. There is a difference in the condition of SLE patients due to the formation of autoantibodies and chronic inflammation.[15] One study reported that in SLE patients, there is an abnormality in macrophages, with a higher prevalence of M1 macrophages compared to M2 macrophages. M1 macrophages are more induced by Gamma Interferon and LPS and play a larger role in inflammation, while M2 macrophages, induced by IL-4 and IL-13, are more involved in cell repair. This imbalance makes it difficult to clear dead cell debris, further exacerbating the inflammatory condition in SLE patients.[16] Additionally, the formation of antibodies against platelet antigens increases the destruction of platelets in the peripheral blood and spleen. The formation of antibodies against Erythropoietin (EPO) and its receptors also worsens the thrombocytopenia in SLE patients infected with diphtheria.[17]

The management of diphtheria in this patient was carried out according to the guidelines provided by the WHO, using ADS 40,000 IU, as the patient was diagnosed with laryngeal diphtheria.[18] The patient was also treated with erythromycin 500 mg until the 7th day of treatment, and clinical and laboratory improvements were observed, leading to the patient's discharge from the hospital.

CONCLUSION

In this case, the SLE of the patient presented clinical features of severe thrombocytopenia; it was considered as mild SLE alongside a C. diphtheria infection. The instruments for measuring disease activity in SLE patients should be adapted to the clinical features observed in this patient. In this way, these tools can be used more broadly, especially in developing countries with remote areas needing thorough assessments for SLE patients. Thus, the hematological abnormalities in this patient may not only have been caused by disease activity but also by opportunistic infections, to which immunocompromised patients are highly susceptible. SLE patients, therefore, require detailed evaluations. This infection could have been hematologically induced or could stem from the underlying SLE condition. The exact interrelationship between hematological disorders and infections in SLE patients is not yet fully understood.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Patient has provided informed consent for the writing of this article.

CONFLICTS OF INTEREST

We have no conflict of interest

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We have no source of funding

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AUTHOR CONTRIBUTION

Conceptualization: MJTA; Data Curation: MJTA; Formal Analysis: MJTA; Investigation: MJTA; Project Administration: MJTA; Resources: MJTA; Methodology: MJTA; Software: MJTA; Visualization: MJTA; Supervision: HK; Validation: HK; Writing – Original Draft Preparation: MJTA; Writing – Review & Editing: HK. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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